American Red Cross

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20857

RE: Draft Guidance for Industry: Revised Recommendations for Donor and Product Management Based on Screening Tests for Syphilis. [68 FR 38083-38084, June 26, 2003; Docket No. 2003D-0236]

Dear Docket Officer:

The American Red Cross (Red Cross) appreciates this opportunity to provide public comments concerning the Food and Drug Administration's Draft Guidance titled "*Revised Recommendations for Donor and Product Management Based on Screening Tests for Syphilis*" (hereafter, referred to as *The Draft Guidance*).

The Red Cross is committed to the safety of donors and patients, and to meet the best interests of the public we serve. The Red Cross, through its 36 Blood Services regions, supplies approximately half of the nation's blood for transfusion needs. The plasma donated by Red Cross' volunteers is recovered from whole blood and further processed or fractionated into plasma derivatives.

The Red Cross appreciates FDA's efforts to provide revised recommendations for testing blood donors for syphilis, and for proposing ways to enable the Red Cross and other blood suppliers to maximize the availability of blood and blood products by using blood and blood components for transfusion purposes from some donors who have reactive, but unconfirmed, screening tests for syphilis.

The Red Cross tests over 6 million donations for syphilis annually, in accordance with the requirement in 21 CFR §§ 640.40(i) and 640.5(a). All testing is performed by our National Testing Laboratories (NTLs) which are certified under the Clinical Laboratory Improvement Acts (CLIA) for such testing. Our routine syphilis testing algorithm includes an initial specific treponemal screening test, the PK-TP assay, performed on the

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Olympus PK 7200 automated blood processing instrument.[1] Donations that have a reactive screening test for syphilis are not used for transfusion, in accordance with FDA's Final Rule, "Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents," issued on June 11, 2001.

Screening-test reactive donations are further tested using a specific enzyme immunoassay (EIA) for IgG antibodies to *T. pallidum* as a confirmatory test. If the EIA is equivocal *or* positive, and the donation sample was originally tested by the routine algorithm (PK-TP screening test), the donation sample is further tested by the non-treponemal Rapid Plasma Reagin (RPR) test to determine whether the syphilis infection is likely active or occurred in the past. These confirmatory and additional tests are done in order to provide more useful information to donors and their physicians about the meaning of the test results and the possible need for treatment. All donors who have reactive syphilis screening test results are notified, in writing, according to the requirement in 21 CFR 610.41 (a), using letters and fact sheets that have been developed and approved by our medical and scientific staff at Biomedical Headquarters.

While we do not disagree with the scientific merit of the recommendations of *The Draft Guidance*, we offer the following comments for your consideration.

C. Release for Transfusion of Units Negative for Syphilis in a Confirmatory Test.

The testing algorithm proposed in section B "Donor Testing and Management, When Using Treponemal-Based Screening Assays as the Test of Record for the Detection of Syphilis" is consistent with the routine testing algorithm currently used by the Red Cross; however, Red Cross considers the approach described in section C, "Release for Transfusion of Units Negative for Syphilis in a Confirmatory Test," impractical. According to the Draft Guidance, FDA recommends that blood providers release for transfusion blood products prepared from donations that test reactive by the PK-TP and non-reactive by a confirmatory test (EIA) and reflect these test results on product labels. While this approach would allow the salvage of some blood donations that are most likely not infectious for *T. pallidum*, Red Cross is concerned about the possibility of creating confusion and alarm on the part of hospital employees, recipients and visitors who might read the labels on blood products, including the syphilis test results.

Persons who are not physicians or laboratory personnel, familiar with various syphilis tests and patterns of results obtained at different times after infection and treatment, are not knowledgeable enough to differentiate the significance of screening test and confirmatory test results on product labels. Therefore, we would be concerned about the potential for adverse consequences using this approach, including recipient anxiety, stopping necessary transfusion therapy, general public outcry, and the potential for legal

[1] Only when a donation sample cannot be tested on the Olympus 7200 for operational reasons, is a Rapid Plasma Reagin (RPR) test performed as the syphilis test of record.

action, should a recipient contract syphilis after transfusion through another route of exposure. While it is unfortunate to lose blood products from donations that test reactive on treponemal-specific tests, long after any risk of infectivity of these products is past, the Red Cross does not think that the recommendation proposed to salvage these products can be realistically implemented.

D. Syphilis Testing and Donor and Unit Management Issues Specific to Whole Blood and Components for Transfusion.

Red Cross notes the use of the term "lookback" in this section of *The Draft Guidance* in association with the retro-active retrieval of in-date products, if donors provide a history of syphilis within the last 12 months or are test reactive or confirmed positive for syphilis on subsequent donations. Red Cross would suggest that the term "lookback" not be used, unless there are intended actions to be taken, such as identification and retrieval of products from previous donations and notification of consignees and recipients of products. Most persons in the industry understand the term "lookback" to imply these actions. Using the term in a broader sense could create confusion or may be misinterpreted in this and other contexts.

Figure B: Donor testing algorithm when a treponemal-based screening assay is the test of record and establishment conducts confirmatory testing.

Red Cross appreciates the flow charts accompanying *The Draft Guidance*, which help to facilitate understanding of the various testing algorithms. Our current routine testing approach uses a treponemal-based screening test (PK-TP); therefore, the flow chart labeled Figure B, applies.

Since the Red Cross' routine screening test of record, the treponemal-specific PK-TP performed on the Olympus automated testing system, remains reactive after successful treatment for syphilis has occurred, donors who are deferred once due to a reactive result on this test are very likely to be deferred again, if they are tested again using the PK-TP test. The only way to avoid this outcome is to test subsequent donations from these donors using a non-treponemal test, such as RPR, which usually reverts to negative once active syphilis infection has resolved. This would mean, however, that Red Cross, and other blood suppliers that use the Olympus, would need to flag these donors and put their samples through an alternative initial syphilis testing algorithm on subsequent donations, to avoid having reactive PK-TP screening test results on these donations. These alternative tests would need to be done manually and their accuracy would rely on selecting the correct samples for testing. Entry of test results into the automated data management system would represent another manual activity.

Red Cross has created state-of-the-art testing laboratories that are highly automated and intended for high-volume testing. Our operations are designed in order to eliminate, in so far as possible, the risk of errors in testing and data management. Any diversion from our

normal testing algorithms that requires selection of samples and manual testing and data entry we view as creating a significant opportunity for error; therefore, we prefer to avoid deviation from the routine testing algorithms and manual testing, whenever possible.

For this reason, Red Cross would not want to consider the adoption of a routine alternative testing algorithm for a relatively small number of previously PK-TP reactive donors, in order to salvage the products from their subsequent donations. This is unfortunate, since we fully believe that such donations are "safe" with respect to syphilis infectivity. We further realize that repeated deferrals create substantial donor relations problems. However, we believe that the possibility of errors created by instituting a special testing algorithm for certain donors is a much more significant problem than potential problems with donor relations or the loss of additional products from these donations. Therefore, while we appreciate the FDA's attempt to provide an approach to salvage products from these donations, Red Cross would not be able to realistically implement this approach in our current operations. We most likely would continue to repeatedly defer these donors based on reactive PK-TP results, even if *The Draft Guidance* is finalized with this alternative testing option.

We would request that FDA make it clear that donors who test reactive on the PK-TP screening test and negative on the EIA confirmatory test do not need to be deferred. Since these donors are not infectious (and their donations could, with appropriate labeling, be used for transfusion, according to *The Draft Guidance)*, it seems contradictory to defer them for twelve months and place them into the Donor Deferral Register (DDR), as is our current practice. While these donors need to be informed about their test results and perhaps encouraged not to donate, since they will most likely have reactive PK-TP results on subsequent donation samples, Red Cross would prefer not to place them into the official DDR file, since this is objectionable to some donors.

The Red Cross appreciates this opportunity to provide public comments on *The Draft Guidance*. If you have any further questions or require follow-up, please contact Barbara M. Peoples, Director, Technical Policy and Promotion at 202-303-5212 (phone), 202-303-0106 (fax) or peoplesb@usa.redcross.org (e-mail).

Sincerely,

Kathryn J. Waldman
Vice President
Regulatory Compliance & Quality Systems;
and Chief Compliance Officer